PATENT COOPERATION TREATY

From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: JANE MASSEY LICATA LICATA & TYRRELL 66 E. MAIN STREET MARLTON NJ 08053 Docket System Status Report Dacket Book M= 3/9/02

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

(PCT Rule 71.1)

Date of Mailing (day/month/year)

260CT 2001

Applicant's or agent's file reference

International application No.

PCT/US00/00583

RTSP-0048

IMPORTANT NOTIFICATION

International filing date (day/month/year)

Priority Date (day/month/year)

10 JANUARY 2000

09 SEPTEMBER 1999

Applicant

ISIS PHARMACEUTICALS, INC.

- The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

REMINDER 4.

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume Π of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US

Commissioner of Patents and Trademarks

Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

(703) 308-0196

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RTSP-0048	FOR FURTHER ACTION	See Notif Prelimin	
International application No.	International filing date (day)	month/year)	Priority date (day/month/year)
PCT/US00/00588	10 JANUARY 2000		09 SEPTEMBER 1999
International Patent Classification (IPC) Please See Supplemental Sheet.	or national classification and l	PC	
Applicant ISIS PHARMACEUTICALS, INC.			
Examining Authority and is 2. This REPORT consists of a This report is also accombeen amended and are th	total of sheets. panied by ANNEXES, i.e., sheet	according to eets of the descreets containing	ription, claims and/or drawings which have ag rectifications made before this Authority.
		· 	
IV Lack of unity of V X Reasoned statement citations and explain VI Certain documents of the company of the c	nt of report with regard to no invention t under Article 35(2) with regard nations supporting such statem	ovelty, invent ard to novelty, ent	ive step or industrial applicability inventive step or industrial applicability;
Date of submission of the demand	Date	of completion	of this report
05 APRIL 2001		OCTOBER	
Name and mailing address of the IPEA/ Commissioner of Patents and Tradems Box PCT Washington, D.C. 20231		iage	Budges for
Facsimile No. (703) 305-3230	Telep	hone No. (7	703) 308-0196

International application No.

			C17 05007 00505
I. Basis of the report			
1. With regard to the element	ts of the international anni	ication:*	
•	pplication as originally		
	FF	,	
pages1-8	81	·	, as originally filed
pages NO	ONE .		, filed with the demand
pages NO	ONE	, filed with the letter of _	
X the claims:	and 83		
Pages		as amanded (together wit	, as originally filed h any statement) under Article 19
P-6	ONE		, filed with the demand
		d with the letter of	, med with the demand
Pu800	,		
X the drawings:			
	ONE		, as originally filed
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	g part of the description		as originally filed
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nages NO	ONE	filed with the letter of	, mod with the definition
2 3774 14 4 1.1	11 4b1	. d . b	ship Arab paint is the leasure of in which
the international applicati	ion was filed unless othe	erwise indicated under this item.	this Authority in the language in which
These elements were avai	ilable or furnished to this	Authority in the following language _	which is:
the language of a t	translation furnished for	or the purposes of international se	earch (under Rule 23.1(b)).
		ational application (under Rule 48	
	translation furnished for	the purposes of international prelimin	ary examination (under Rules 55.2 and
or 55.3).			
e e			national application, the international
preliminary examination	n was carried out on th	ne basis of the sequence listing:	
x contained in the in	nternational application	n in printed form.	
filed together with	the international appl	lication in computer readable form	n.
	ently to this Authority		
ш.		in computer readable form.	
The statement that international application	the subsequently furnish ation as filed has been	hed written sequence listing does ne furnished.	ot go beyond the disclosure in the
The statement that the been furnished.	he information recorded	in computer readable form is identical	al to the writen sequence listing has
4 X The amendments I	have resulted in the ca	incellation of:	
X the descripti	on, pages NONE		
X the claims,	NONE		
	s, sheets /fig NONE		
	-	ne amendments had not been made, si	nce they have been considered to 20
		n the Supplemental Box (Rule 70.2(c	•
* Replacement sheets which	have been furnished to th	e receiving Office in response to an inv	vitation under Article 14 are referred to not contain amendments (Rules 70.16
·	containing such amendme	ents must be referred to under item .	I and annexed to this report.

International application No.

statement			
Novelty (N)	Claims	5- 20	Y
• . ,	Claims	1 and 2	N
Inventive Step (IS)	Claims	3, 4, and 16-20	Y
interior coop (10)	Claims	1, 2, and 5-15	N
Industrial Applicability (IA)	Claims	NONE	Y
	Claims	HONE	N
preceding paragraph and further in view 1998, pages 69-76). The instant invention XIAP. WO 98/85693 disclose antisense oligonucleotides which one would use oligonucleotides.	on comprises variou targeted to XIAP	Cook discloses various modifications t	gonucleotides targeted hat are used in antisen
1998, pages 69-76). The instant inventic XIAP. WO 98/35693 disclose antisense oligonucleotides which one would use	on comprises various targeted to XIAP for the various best out in PCT Arotides recited in cla	s chemical modifications to antisense oli Cook discloses various modifications t sefits recognized in the art for such m ticle 33(2)-(4), because the prior art doe times 3 and 4 nor does the art teach or f	gonucleotides targeted hat are used in antisen codifications to antisen s not teach or fairly airy suggest methods o
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International application No.

PCT/US00/00583

Sup	pleme	ental	Box
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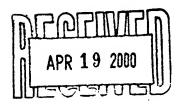
Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below: IPC(7): C07H 21/04; A61K 48/00; C12N 15/00, 15/15/09; C12Q 1/68 and US C1.: 536/23.1, 24.1, 24.5; 435/6, 375, 377, 455; 514/44

Form PCT/IPEA/409 (Supplemental Box) (July 1998)*



From the INTERNATIONAL BUREAU

To

LICATA, Jane, Massey Law Offices of Jane Massey Licata 66 E. Main Street Marlton, NJ 08053 ETATS-UNIS D'AMERIQUE

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

Date of mailing (day/month/year)
07 April 2000 (07.04.00)

Applicant's or agent's file reference
RTSP-0048

International application No.
PCT/US00/00583

International publication date (day/month/year)
Not yet published

Applicant

Important Notification

International filing date (day/month/year)
10 January 2000 (10.01.00)

Priority date (day/month/year)
09 September 1999 (09.09.99)

ISIS PHARMACEUTICALS, INC. et al

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the
 International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise
 indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority
 document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- 2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- 3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- 4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date

Priority application No.

Country or regional Office or PCT receiving Office

Date of receipt of priority document

09 Sept 1999 (09.09.99)

09/392,580

US

28 Marc 2000 (28.03.00)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland

Authorized officer

Tessadel PAMPLIEGA Tol

A jag

Facsimile No. (41-22) 740.14.35

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY JANE MASSEY LICATA LICATA & TYRRELL 66 E. MAIN STREET WRITTEN OPINION MARLTON NJ 03055 Docket System (PCT Rule 66) Status Report Docket Book Date of Mailing (day/month/year) Applicant's or agent's file reference REPLY DUE within TWO months RTSP-0048 from the above date of mailing International application No. International filing date (day/month/year) Priority date (day/month/year) PCT/US00/00583 10 JANUARY 2000 09 SEPTEMBER 1999 International Patent Classification (IPC) or both national classification and IPC Please See Supplemental Sheet. Applicant ISIS PHARMACEUTICALS, INC. 1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority. 2. This opinion contains indications relating to the following items: Basis of the opinion H Priority III Non-establishment of opinion with regard to novelty, inventive step or industrial applicability Lack of unity of invention Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement Certain documents cited VII Certain defects in the international application VIII Certain observations on the international application 3. The applicant is hereby invited to reply to this opinion. When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d). By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. How? For the form and the language of the amendments, see Rules 66.8 and 66.9. Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis. For an informal communication with the examiner, see Rule 66.6. If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks

Box PCT Washington, D.C. 20231

Facsimile No. (703) 305-3230

4. The final date by which the international preliminary

examination report must be established according to Rule 69.2 is: 09 JANUARY 2002

Authoriz

(703) 308-0196

Form PCT/IPEA/408 (cover sheet) (July 1998)*

International application No.

I. B	asis of t	he opinion						
1. With	negard to	o the elements of the international applica	tion:*					
\mathbf{x}								
x		cription:						
	pages	1-81	, as originally filed					
	pages	NONE	, filed with the demand					
	pages _	NONE	, filed with the letter of					
[]	the clai							
X	pages _		, as originally filed					
	pages		, as amended (together with any statement) under Article 19					
	pages _	NONE	, filed with the demand					
	pages _	NONE , filed	with the letter of					
	*La dens							
X	the draw	NAME	, as originally filed					
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	pages _	NONE	, filed with the letter of					
X		nence listing part of the description:						
			, as originally filed					
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2. With	n regard to	the language, all the elements marked a	above were available or furnished to this Authority in the language in which					
The	internations se elemen	nal application was filed, unless otherwints were available or furnished to this Au	thority in the following language which is:					
			the purposes of international search (under Rule 23.1(b)).					
H			onal application (under Rule 48.3(b)).					
7								
Ш	the languor 55.3).		purposes of international preliminary examination (under Rules 55.2 and/					
	,							
	_	•	equence disclosed in the international application, the written opinion was					
_	wn on us	e basis of the sequence listing:						
X	containe	ed in the international application in	printed form.					
	filed to	gether with the international applica	tion in computer readable form.					
\sqcap	furnishe	ed subsequently to this Authority in	written form.					
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][• • •	l written sequence listing does not go beyond the disclosure in the					
Ш	internati	onal application as filed has been fur	nished.					
	The state been fun	ement that the information recorded in nished.	computer readable form is identical to the writen sequence listing has					
₄ X	The am	endments have resulted in the canc	ellation of:					
ئـتـا .4	অ	NONE						
		le description, pages						
		ne claims, Nos. NONE						
		e drawings, sheets/fig NONE						
5.		nion has been drawn as if (some of) the the disclosure as filed, as indicated in the	amendments had not been made, since they have been considered to go the Supplemental Box (Rule 70.2(c)).					
•		theets which have been furnished to the reas "originally filed".	eceiving Office in response to an invitation under Article 14 are referred to					

International application No.

statement			
Novelty (N)	Claims	3-2 0	
	Claims	1 and 2	N
Inventive Step (IS)	Claims	3, 4, and 16-20	Ү
	Claims	1, 2, and 5-15	N
Industrial Applicability (IA)	Claims	1-90	Y
	Claims	NONE	N
citations and explanations			
Claims 1 and 2 lack novelty under PCT Artic	cle 33(2) as bein	g anticipated by WO 98/35693 (UNIVER	SITY OF OTTOWA
WO 98/85695 discloses nucleic aci- of apoptosis, and disclose, at pages 15 and 14 antisense lengths such as 8-25 nucleotides. E.	for example, re		antisense and preferr
antisense lengths such as 6-25 nucleotiues. E.	xampie 9 and pa	ge 45 disclose that antisense to AIAr have	e Deen made and teste
Claims 5-15 lack an inventive step under PC preceding paragraph and further in view of Co	ook S.T. (Antise		search and Applicatio
1998, pages 09-70). The instant invention co	omprises various	chemical modifications to antisense ongo	
XIAP. WO 98/55695 disclose antisense tar oligonucleotides which one would use for t	geted to XIAP.	Cook discloses various modifications that	t are used in antisen
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International application No.

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International application No.

PCT/US00/00583

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(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below: IPC(7): C07H 21/04; A61K 48/00; C12N 15/00, 15/15/09; C12Q 1/68 and US Cl.: 536/23.1, 24.1, 24.5; 435/6, 375, 377, 455; 514/44

INTERNATIONAL SEARCH REPORT

International application No. PCT/US00/00583

IPC(7) US CL According	ASSIFICATION OF SUBJECT MATTER: C07H 21/04; A61K 48/00; C12N 15/00, 15/15/0:536/23.1, 24.1, 24.5; 435/6, 375, 377, 455; 514/to International Patent Classification (IPC) or to bot	44	
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U.S. :	documentation searched (classification system follow 536/23.1, 24.1, 24.5; 435/6, 375, 377, 455; 514/4	4	
Documenta NONE	tion searched other than minimum documentation to the	e extent that such documents are included	in the fields scarched
	data base consulted during the international search (in MEDLINE BIOSIS, EMBASE, CAPLUS, SCISEAR		e, search terms used)
C. DOC	CUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where a	ppropriate, of the relevant passages	Relevant to claim No.
X	WO 98/35693 A2(UNIVERSITY OF pages 13-14, 45 and Example 9.	OTTOWA) 20 August 1998,	1, 2
Y	pages to try to and Example 7.		5-15
Y	COOK S.T. Antisense Medicinal (Research and Application. Edited by Springer. 1998, pages 69-76, entire decimal)	5-15	
	·		
Furth	er documents are listed in the continuation of Box (See patent family annex.	
"A" doo	ecial estegories of cited documents: cument defining the general state of the art which is not considered be of particular relevance	*T* later document published after the inte date and not in conflict with the appl the principle or theory underlying the	cation but cited to understand
"L" doc	lier document published on or after the international filing date cument which may throw doubts on priority claim(s) or which is ad to establish the publication date of another citation or other cial reason (as specified)	"X" document of particular relevance; the considered novel or cannot be consider when the document is taken alone "Y" document of particular relevance; the	red to involve an inventive step
-	sument referring to an oral disclosure, use, exhibition or other	considered to involve an inventive combined with one or more other such being obvious to a person skilled in t	step when the document is documents, such combination
	rument published prior to the international filing date but later than priority data claimed	*A* document member of the same patent	fam ily
Date of the	actual completion of the international search	Date of mailing of the international sea 2.9 MAR 2000	rch report
Commission Box PCT	nailing address of the ISA/US ner of Patents and Trademarks	Authorized officer SEAN MCGARRY	ab,
-	L D.C. 20231	Telephone No. (703) 208 2104	Arr

PATENT COOPERATION TREATY

PCT

REC'D 3 0 OCT 2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

PCT

(PCT Article 36 and Rule 70)

Applicant of GL C	T		
Applicant's or agent's file reference RTSP-0048	FOR FURTHER ACTION	Prelimina	cation of Transmittal of International ary Examination Report (Form
International application No.	International filing date (day	PCT/IPEA /month/year)	Priority date (day/month/year)
PCT/US00/00588	10 JANUARY 2000		09 SEPTEMBER 1999
International Patent Classification (IPC) Please See Supplemental Sheet.	or national classification and	IPC	<u></u>
Applicant ISIS PHARMACEUTICALS, INC.			
2. This REPORT consists of a This report is also accomp been amended and are the	transmitted to the applican total of sheets. panied by ANNEXES, i.e., sheet basis for this report and/or slon 607 of the Administrative.	t according to eets of the descreets containin	ription, claims and/or drawings which have g
3. This report contains indications			
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I X Basis of the repor	t		
II Priority			
III Non-establishmen	t of report with regard to no	ovelty, inventi	ve.step.or industrial applicability
IV Lack of unity of i		• • • • • • • • • • • • • • • • • • • •	application,
V X Reasoned statement	•	ard to novelty,	inventive step or industrial applicability;
VI Certain documents of			
VII Certain defects in th	e international application		
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Date of submission of the demand	Date	of completion	of this report
05 APRIL 2001		OCTOBER 2	2001
Name and mailing address of the IPEA/U	JS Auth	ofiged officer	Budges /
Commissioner of Patents and Tradema, Box PCT Washington, D.C. 20231		AREN LACOL	DIRCIERE LA
Facsimile No. (703) 305-3230	Telep	hone No. (70	03) 308-0196
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International	application	No.
I A SECONDIAN CONTRACTOR IN CO	application	

I.	В	asis o	f the repo	ort				
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3.						sequence disclos asis of the sequen		nal application, the international
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International application No.

. statement			
Novelty (N)	Claims	3-20	YE
	Claims	1 and 2	NO
Inventive Step (IS)	Claims	3, 4, and 16-20	YE
	Claims	1, 2, and 5-15	NC
Industrial Applicability (IA)	Claims	1-20	YE
	Claims	NONE	NC
preceding paragraph and further in view of C	Cook S.T. (Antise	as being obvious over the prior art as applied in the imnse Medicinal Chemistry. In: Antisense Research and Als chemical modifications to antisense oligonucleotides t	mediatel
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International application No.

PCT/US00/00583

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

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CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below: IPC(7): C07H 21/04; A61K 48/00; C12N 15/00, 15/15/09; C12Q 1/68 and US C1.: 536/23.1, 24.1, 24.5; 435/6, 37 455; 514/44